Amendments to the Specification:

Please replace the Title of the Invention on page 1, lines 1-2, with the following amended Title:

Treatment of Inflammatory Bowel Disease Using ~~Growth Factors~~ Fibroblast Growth Factor CX and FCTRX Polypeptides

Please replace the Related Application paragraph at page 1, lines 2-3 with the following amended paragraph:

This application claims the benefit of priority from U.S. Ser. No. 60/246,206 filed November 6, 2000, now abandoned, the contents of which are incorporated herein in its entirety.

Please replace the paragraph at page 7, lines 15-16 with the following amended paragraph:

FIG. 40 presents bar graphs representing histopathology score ~~differencess~~ differences in mice after various treatments.

Please replace the paragraph at page 7, lines 21-22 with the following amended paragraph:

FIG. 43 presents photomicrographs at 50x in the original image of mouse colon ~~crossections~~ cross-sections. Panel A, DSS plus Vehicle; Panel B, DSS+AB020858; Panel C, Normal mouse.

Please replace the paragraph at page 8, lines 3-4 with the following amended paragraph:

FIG. 50 presents mean colon ~~colon~~ weights as a percent of normal, upon treating mice with varying doses of AB020258.

Please replace the paragraph at page 8, line 29 through page 9, line 4 with the following amended paragraph:

FIG. 62 presents images showing the protective effect of CG53135 on intestinal architecture. Panel A: Small intestine from normal control animal treated iv with vehicle (BSA). Panel. B: Small intestine from indomethacin- treated rat, further treated with vehicle (BSA) iv.

Panel C: Small intestine from indomethacin-treated rat further treated with CG53135, 0.2 mg/kg iv. Sections were stained with H&E and visualized at a magnification of 25). FIG. 62 shows the protective Effect of CG53135 on Intestinal ~~Architecturein~~ Architecture in indomethacin treated rats. Panel A, normal control; Panel B, disease control (indomethacin treated); Panel C, disease model animal treated with 0.2 mg/kg iv CG53135. Photomicrographs were obtained on sections stained with hemotoxylin and eosin, at 25X magnification.

Please replace the paragraph at page 10, lines 22-26 with the following amended paragraph:

In Europe and the United States, incidence and prevalence of CD is approximately 1-6 and 10-100 cases per 100, 000 population respectively. For UC the incidence and prevalence rates are respectively 2-10 and 35-100 per 100, 000. There is a slight ~~preponderence~~ preponderance in females over males for contracting the disease. UC and CD affect primarily individuals between the ages of 15 and 35 years.

Please replace the paragraph at page 11, lines 5-12 with the following amended paragraph:

The 5-ASAs (sulfasalazine and the sulfa-free agents) are known to alter the immune response by down-~~regulationg~~ regulating antibody secretion and lymphocyte function, inhibit neutrophil and macrophage chemotaxis and protect intestinal epithelium by enhancing expression of heat shock proteins. In addition, they also inhibit the cyclooxygenase and 5-lipoxygenase pathways of arachidonic acid metabolism that may inhibit the release of chemotactic substances (Grisham, M. B. Lancet, 1994, 344:859-861). 5-ASAs are effective therapeutic agents for mild to moderate conditions of UC. However, 5-ASAs are not the drugs of choice for IBD due to their side effects that may include nausea, allergic reactions and reversible oligospermia.

Please replace the paragraph at page 12, lines 6-10 with the following amended paragraph:

Cyclosporine has been effective in the treatment of both CD and UC. Cyclosporine has been particularly shown to be effective in patients with active CD or UC that are resistant or intolerant to ~~corticosteriods~~ corticosteroids (Lichtiger *et al.* New England Journal of Medicine, 1994, 330:1841-1845). The side effects of cyclosporin include reversible or irreversible decrease in renal function, hypertension, tremor, and seizure.

Please replace the paragraph at page 21, lines 10-12 with the following amended paragraph:

PFAM and PROSITE analyses ~~indicte~~ indicate that 30664188.0.99 polypeptide amino acid sequence ~~conatains~~ contains a PDGF domain (aa 272-362) and a N-linked glycosylation site (residue 276).

Please replace the paragraph at page 23, line 17 through page 23, line 4 with the following amended paragraph:

A FCTR3 (also ~~refered~~ referred to within the specification as PDGFD or murine PDGFD or mPDGFD) nucleic acid and polypeptide according to the invention includes the nucleic acid and encoded polypeptide sequence shown in Table 4 (SEQ ID NO:7 and 8). The start and stop codons are shown in bold. The FCTR3 nucleic acid sequence was identified from a murine brain library. The predicted open reading frame codes for a 370 amino acid long secreted protein. The FCTR3 has a predicted molecular weight of 42,808 daltons and a pI of 7.53. Protein structure analysis using PFAM and PROSITE identified the core PDGF domain within the FCTR3 polypeptide sequence.

Please replace the paragraph at page 24, lines 9-15 with the following amended paragraph:

A FCTR4 (also ~~refered~~ referred to within the specification as PDGFD or murine PDGFD or mPDGFD) nucleic acid and polypeptide according to the invention includes the nucleic acid and encoded polypeptide sequence shown in Table 5 (SEQ ID NO:9 and 10). The start and stop codons are shown in bold. The FCTR4 nucleic acid sequence was identified from a murine brain library and is a splice variant of FCTR3. FCTR4 has an internal stop codon in comparison with FCTR3. See Table 8. Unlike FCTR3, however, FCTR4 lacks a significant portion of the PDGF-like domain. See Table 9.

Please replace the paragraph at page 25, lines 3-7 with the following amended paragraph:

A FCTR5 (also ~~refered~~ referred to within the specification as PDGFD or human PDGFD or hPDGFD or clone pCR2.1-S852_2B) nucleic acid and polypeptide according to the invention includes the nucleic acid and encoded polypeptide sequence of FCTR5 and is shown in Table 6

(SEQ ID NO:11 and SEQ ID NO:12). The FCTR5 nucleic acid sequence was identified as a splice variant of FCTR1.

Please replace the paragraph at page 25, line 15 through page 26, line 2 with the following amended paragraph:

A FCTR6 (also ~~refered~~ to within the specification as PDGFD or human PDGFD or hPDGFD) nucleic acid and polypeptide according to the invention includes the nucleic acid and encoded polypeptide sequence of FCTR6 and is shown in Table 7 (SEQ ID NO:13 and SEQ ID NO:14). The FCTR6 sequence (also referred to as clone pCR2.1-S869_4B) was identified as a splice variant of FCTR1.

Please replace the paragraph at page 34, lines 1-8 with the following amended paragraph:

The similarity between FCTRX polypeptides and PDGF polypeptides suggests that FCTRX nucleic acids and their encoded polypeptides can be used in various therapeutic and diagnostic applications. For example, FCTRX nucleic acids and their encoded polypeptides can be used to treat cancer, cardiovascular and fibrotic diseases and diabetic ulcers. In addition, FCTRX nucleic acids and their encoded polypeptides will be therapeutically useful for the prevention of aneurysms and the ~~the~~ acceleration of wound closure through gene therapy. Furthermore, FCTRX nucleic acids and their encoded polypeptides can be utilized to stimulate cellular growth.

Please replace the paragraph at page 79, lines 11-28 with the following amended paragraph:

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, ~~Cremophor EL~~™ CREMOPHOR EL® (non-ionic solubilizer and emulsifier) (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can

be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Please replace the paragraph at page 86, lines 6-16 with the following amended paragraph:

The cell-free assays of the invention are amenable to use of both the soluble form or the membrane-bound form of FGF-CX and/or FCTRX protein. In the case of cell-free assays comprising the membrane-bound form of FGF-CX and/or FCTRX protein, it may be desirable to utilize a solubilizing agent such that the membrane-bound form of FGF-CX and/or FCTRX protein is maintained in solution. Examples of such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n-dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl-N-methylglucamide, ~~Triton® X-100, Triton® X-114, Thesit®~~ TRITON®-X-100 (nonionic detergent), TRITON®-X-114 (nonionic detergent), THESIT® (nonionic detergent), (Isotridecypoly(ethylene glycol ether)$_n$, N-dodecyl--N,N-dimethyl-3-ammonio-1-propane sulfonate, 3-(3-cholamidopropyl) dimethylamminiol-1-propane sulfonate (CHAPS), or 3-(3-cholamidopropyl)dimethylamminiol-2-hydroxy-1-propane sulfonate (CHAPSO).

Please replace the paragraph at page 104, lines 8-20 with the following amended paragraph:

Diseases and disorders that are characterized by increased (relative to a subject not suffering from the disease or disorder) levels or biological activity may be treated with Therapeutics that antagonize (*i.e.*, reduce or inhibit) activity. Therapeutics that antagonize activity may be administered in a therapeutic or prophylactic manner. Therapeutics that may be

utilized include, but are not limited to: (*i*) an aforementioned peptide, or analogs, derivatives, fragments or homologs thereof; (*ii*) antibodies to an aforementioned peptide; (*iii*) nucleic acids encoding an aforementioned peptide; (*iv*) administration of antisense nucleic acid and nucleic acids that are "dysfunctional" (*i.e.,* due to a heterologous insertion within the coding sequences of coding sequences to an aforementioned peptide) that are utilized to "knockout" ~~endoggenous~~ endogenous function of an aforementioned peptide by homologous recombination (*see, e.g.,* Capecchi, 1989. *Science* 244: 1288-1292); or (*v*) modulators (*i.e.*, inhibitors, agonists and antagonists, including additional peptide mimetic of the invention or antibodies specific to a peptide of the invention) that alter the interaction between an aforementioned peptide and its binding partner.

Please replace the paragraph at page 110, line 27 through page 111, line 3 with the following amended paragraph:

The BglII-XhoI fragment containing the FGF-CX sequence was isolated from TA-AB02085-S274-F19 (Example 2) and subcloned into the BamHI-XhoI digested pCEP4/Sec to generate the expression vector pCEP4/Sec-FGF-CX. The pCEP4/Sec-FGF-CX vector was transfected into 293 cells using the ~~LipofectaminePlus~~ LIPOFECTAMINEPLUS® (transfection reagent) reagent following the manufacturer's instructions (Gibco/BRL/Life Technologies, Rockville, MD). The cell pellet and supernatant were harvested 72 hours after transfection and examined for FGF-CX expression by Western blotting (reducing conditions) with an anti-V5 antibody. FIG. 1 shows that FGF-CX is expressed as a polypeptide having an apparent molecular weight (Mr) of approximately 34 kDa proteins secreted by 293 cells. In addition a minor band is observed at about 31 kDa.

Please replace the paragraphs at page 112, lines 1-15 with the following amended paragraphs:

In addition to secretion of FGF-CX into conditioned media, it also found to be associated with the cell pellet/ECM (data not shown). Since FGFs are known to bind to heparin sulfate proteoglycan (HSPG) present on the surface of cells and in the extracellular matrix (ECM), the inventors investigated the possibility that FGF-CX was sequestered in this manner. To this end,

FGF-CX-transfected cells were extracted by treatment with 0.5 ml DMEM containing 100 μM suramin, a compound known to disrupt low affinity interactions between growth factors and HSPGs (La Rocca, R.V., Stein, C.A. & Myers, C.E. (1990) *Cancer Cells* 2, 106-115), for 30 min at 4^0C. The suramin-extracted conditioned media was then harvested and clarified by ~~centrifigation~~ centrifugation (5 min; 2000 X g).

The conditioned media and the suramin extract were then mixed with equal volumes of 2X gel-loading buffer. Samples were boiled for 10 min, resolved by SDS-PAGE on 4-20% gradient polyacrylamide gels (Novex, Dan Diego, CA) under reducing conditions, and transferred to ~~nitrocelluose~~ nitrocellulose filters (Novex). Western analysis was performed according to standard procedures using HRP-conjugated anti-V5 antibody (Invitrogen) and the ECL detection system (Amersham Pharmacia Biotech, Piscataway, NJ).

Please replace the paragraph at page 113, lines 12-24 with the following amended paragraph:

A dose response experiment for incorporation of BrdU was carried out using human renal carcinoma cells (786-0; American Type Culture Collection, Manassas, VA). 293-EBNA cells (Invitrogen) were transfected using ~~Lipofectamine 2000~~ LIPOFECTAMINE 2000® (transfection reagent) according to the manufacturer's protocol (Life Technologies, Gaithersburg, MD). Cells were supplemented with 10% fetal bovine serum (FBS; Life Technologies) 5 hr post-transfection. To generate protein for BrdU and growth assays (Example 10), cells were washed and fed with Dulbecco's modified Eagle medium (DMEM; Life Technologies) 18 hr post-transfection. After 48 hr, the media was discarded and the cell monolayer was incubated with 100 μM suramin (Sigma, St. Louis, MO) in 0.5 ml DMEM for 30 min at 4^0C. The suramin-extracted conditioned media was then removed, clarified by centrifugation (5 min; 2000 X g), and subjected to TALON metal affinity chromatography according to the manufacturer's instructions (Clontech, Palo Alto, CA) taking advantage of the carboxy-terminal polyhistidine tag. Retained fusion protein was released by washing the column with imidazole.

Please replace the heading at page 115, lines 12-13 with the following amended heading:

Example 12. Molecular cloning of a mature FCTR1 form (30664188.0.m99) polypeptide from ~~eline~~ clone 30664188.0.99

Please replace the paragraph at page 117, lines 8-22 with the following amended paragraph:

The EcoRI-XhoI fragment containing the 30664188.m99 sequence was isolated from 30664188-S311a (Example 12) and subcloned into the vector pE28a (Novagen, Madison, WI) to give the plasmid pET28a-30664188. Subsequently, pET28a-30664188 was partially digested with BamHI restriction enzyme, and then completely digested with XhoI. A fragment of 1.1 kb was isolated and ligated into BamHI-XhoI digested pCEP4/Sec (Example 3) to generate expression vector pCEP4/Sec-30664188.m99. The pCEP4/Sec-30664188.m99. vector was transfected into human embryonic kidney 293 cells (ATCC No. CRL-1573, Manassas, VA) using the ~~LipofectaminePlus~~ LIPOFECTAMINEPLUS® (transfection reagent) following the manufacturer's instructions (Gibco/BRL/Life Technologies, Rockville, MD). The cell pellet and supernatant were harvested 72 hours after transfection and examined for expression of the 30664188.m99 protein by Western blotting of an SDS-PAGE run under reducing conditions using an anti-V5 antibody. FIG. 10 shows that 30664188.m99 is expressed as three discrete protein bands of apparent molecular weight 50, 60, and 98 kDa secreted by 293 cells. The 50 kDa band migrated at a sized expected for a monomer glycosylated form of 30664188.m99, and the 98 kDa band migrated at a size consistent with a dimer of the monomer form.

Please replace the paragraph at page 117, line 24 through page 118, line 3 with the following amended paragraph:

HEK 293 cells were grown in Dulbecco's modified eagle's medium (DMEM)/10% fetal bovine serum medium to 90 % confluence. The cells were transfected with pCEP4sec or pCEP4sec/30664188.m99 using ~~Lipofectamine 2000~~ LIPOFECTAMINE 2000® (transfection reagent according to the manufacturer's specifications (Gibco/BRL/Life Technologies, Rockville, MD). Transfected cells were incubated for 2 days with DMEM and conditioned medium was prepared by collection of cell supernatants. The conditioned medium was enriched by Talon metal affinity chromatography (Clontech, Palo Alto, CA). Briefly, 7 ml of conditioned medium was incubated with 1 ml of Talon metal affinity resin in spin columns. The spin columns were washed twice with one ml of PBS. The columns were then eluted twice with 0.65 ml of PBS/0.5M imidazole pH 8.0 and the eluates pooled. Imidazole was removed by buffer exchange

dialysis into PBS using Microcon centrifugal filter devices (Millipore Corp., Bedford, MA). The enriched gene products were stored at 4°C.

Please replace the paragraph at page 118, lines 4-15 with the following amended paragraph:

The purified protein obtained was subjected to SDS-PAGE under reducing conditions and probed with an anti-V5 antibody, which was detected with an enzyme label. The results of two separate transfection and purification runs are shown in the gels. They show that the product is a mixture of V5-containing polypeptides. The largest has an apparent molecular weight of about 50 kDa (FIG. 11, Panel B). The program ProSite predicts one N-glycosylation site in the mature protein. Glycosylation may explain the apparent molecular weight found. Thus the 50kDa band is consistent with the length expected for full length gene product. Other bands, preponderantly having apparent molecular weights of about 20-25 kDa also arise. These are presumed to be the result of proteolysis occurring either intracellularly within the 293 cells or extracellularly after secretion from them. In another run (not shown) the broad band extending from about 6 kDa to about 14 kDa is ~~reolved~~ resolved into two bands of about 7-8 kDa and about 10 kDa.

Please replace the paragraph at page 129, line 29 through page 130, line 15 with the following amended paragraph:

Colonic shortening (due to inflammation and mucosal tissue loss) was inhibited 40% by treatment with AB020858. This gross observation was strongly supported by the histologic observations of mucosal epithelial preservation in the crypts, colonic glands and surface epithelium (see FIGS. 42 and 43). In FIG. 42, viewed at 400x in the original images, the normal colonic mucosa has uniform glandular architecture and no submucosal edema (upper left). The disease control has no mucosal glands and surface epithelium, exposing blood vessels of the severely inflamed lamina propria to the lumen and resulting in hemorrhage (upper right). ~~Itreatment~~ Treatment with CG53135 preserves mucosal integrity and results in decreased epithelial loss and reduced inflammation in the lamina propria (lower left). Treatment with CG52053 decreases epithelial loss and mucosal inflammation, although to a lesser degree than treatment with CG53135 (lower right). In FIG. 43, viewed at 50x in the original images, the normal control shows normal colonic mucosa with uniform glandular architecture and no

submucosal edema (upper left). DSS-induced colitis results in loss of glandular architecture and edema that separates the mucosa from the outer muscle layers (upper right). Treatment with CG53135 inhibits the severe mucosal changes and submucosal edema induced by DSS (lower left). Treatment with CG52053 results in some inhibition of inflammation and loss of glandular architecture but no inhibition of submucosal edema (lower right). This histologic evidence of mucosal protection corroborates the dramatic necropsy observation that very little hemorrhagic diarrhea occurs.

Please replace the paragraph at page 133, line 23 through page 134, line 5 with the following amended paragraph:

Study Design. Female Lewis rats (Harlan, Indianapolis, IN) weighing 175-200 g were acclimated for 8 days (Day -8 through Day -1). Rats were divided into 8 treatment groups: four groups receiving CG53135 (three groups iv and one group sc), two iv controls for normal and the disease model, and two sc controls for normal and the disease model. On Day -1, treatments with CG53135 or vehicle were initiated and continued through Day 4. CG53135 was injected iv (tail vein) at doses of 5, 1 or 0.2 mg/kg, or 1 mg/kg sc; vehicle controls were injected with BSA (5 mg/mL in PBS + 1M L-~~agrinine~~ arginine). On Days 0 and 1 rats were treated with indomethacin (Sigma Chemical Co., St. Louis, MO; 7.5 mg/kg doses) in order to induce gross and histopathologic intestinal alterations similar to those occurring in Crohn's Disease. Indomethacin was prepared in 5% sodium bicarbonate. On Day 5, rats were injected with a single ip dose of 50 mg/kg 5-bromo-2'deoxyuridine (BrdU, Calbiochem, LaJolla, CA) 1 hour prior to necropsy in order to pulse label proliferating cells in the intestine and spleen. Following termination, a 10 cm section of jejunum in the area at risk for lesions was weighed, given a gross pathology score, and then collected into formalin for histopathologic evaluation and scoring of necrosis and inflammation. Blood was collected for CBC analysis.

Please replace the paragraph at page 136, lines 15-27 with the following amended paragraph:

BrdU labeling was carried out by injecting 50 mg/kg 1hr prior to necropsy. In the small intestine from a normal control animal, normal pattern of crypt labeling is seen at 100X (FIG. 63, Panel A). BrdU incorporation in the disease model was decreased or absent in ~~eptithelial~~

epithelial cells in mucosal areas of necrosis, but increased in ~~subajacent~~ subjacent inflammatory tissue in which fibroblast labeling was prominent (FIG. 63, Panel B, visualized at 50X). Focal mucosal necrosis (arrow) is delineated by an absence of BrdU immunostaining as well as severe infiltration of inflammatory cells and fibroblast proliferation. Small intestine from a rat treated with indomethacin + CG53135 0.2 mg/kg iv shows an absence of crypt labeling, but relatively intact mucosa (arrow in FIG. 63, Panel C, visualized at 50X). ~~Subadjacent~~ Subjacent smooth muscle and mesentery is only mildly infiltrated with inflammatory cells, compared with that seen in the disease control (Panel B). In certain animals treated with CG53135, in which preservation of mucosal integrity occurred, increased crypt labeling was also observed; this is in the direction found in the normal control.